



Efficacy of cannabinoids in pharmaco-resistant epilepsy: A narrative review of the literature

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SUMMARY

Epilepsy is a common neurological disorder that affects approximately 1% of the world's population. About one third of those patients suffer from treatment-resistant epilepsy (TRE), defined as failure to stop seizures despite adequate trials of at least two medications at therapeutic dosages. There has been a growing interest in the development of novel antiepileptic drugs with different mechanisms of action. This narrative review, based on 42 references retrieved from Scopus and Medline, discusses the scientific data from human and animal studies regarding the efficacy of cannabis-based treatment for epilepsy. Benefits have been described in pre-clinical and clinical studies in children, but ongoing research will clarify the real role of cannabinoids in TRE.

KEY WORDS

Cannabis; Drug Resistant Epilepsy; Review

RESUMEN

Eficacia de los cannabinoides en epilepsia refractaria: Una revisión narrativa de la literatura

La epilepsia es un desorden neurológico común que afecta aproximadamente al 1% de la población mundial. Alrededor de un tercio de los pacientes sufren de epilepsia resistente al tratamiento,

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Received: July 19th, 2019

Accepted: November 12th, 2019

How to cite: Ferreiros A, Beltrán-Carrascal E, Restrepo P, Pantoja C, Castañeda-Cardona C, Lasalvia P, et al. Efficacy of cannabinoids in pharmaco-resistant epilepsy: A narrative review of the literature. *Iatreia*. 2020 Abr-Jun;33(2):167-176. DOI 10.17533/udea.iatreia.42.

que se define como la falla de parar las crisis epilépticas a pesar de haber recibido tratamiento con dos medicamentos a dosis terapéuticas. Se ha visto interés en el desarrollo de medicamentos antiepilépticos con diferentes mecanismos de acción. Esta revisión narrativa se basó en 42 referencias extraídas de Scopus y Medline, que discuten hallazgos científicos sobre estudios en humanos y animales acerca de la eficacia del cannabis para el tratamiento de epilepsia. Los beneficios se describieron en estudios pre-clínicos y clínicos en niños, sin embargo investigaciones en curso clarificarán el papel real de los cannabinoides para la epilepsia resistente al tratamiento.

PALABRAS CLAVE

Cannabis; Epilepsia Refractaria; Revisión

INTRODUCTION

Epilepsy affects around 1% of the world population and up to 30% of them suffer from treatment-resistant epilepsy (TRE) ⁽¹⁾. In these patients, at least two tolerated, appropriately chosen and used antiepileptic drug (AED) regimens at therapeutic dosages fail to achieve sustained seizure remission ⁽¹⁻³⁾. Despite the availability of more than 20 AED and the continued research, discovery and approval of many new treatments with different mechanisms of action for epilepsy, the proportion of patients with TRE remains high ⁽¹⁾. Furthermore, the safety and side-effect profile of AEDs remains a concern. Although it has improved in the past decades, central nervous system (CNS) related side effects are common, affecting quality of life ⁽⁴⁾. Therefore, patients and families often seek alternative medication, which explains the rising interest in cannabis-based treatment for epilepsy.

Cannabis has been used medicinally for thousands of years. It was known and used by the Sumerians, Assyrians, Chinese, and Indians in a number of diseases as far back as the second millennium BC ⁽⁵⁾. In the mid-1800s, William O'Shaughnessy reported the use of cannabis for the treatment of epilepsy. In the middle-to the late 19th century, two prominent English neurologists, Reynolds and Gowers, also noted benefits of cannabis for the treatment of epilepsy. Over the last 50 years, the main constituents of cannabis have been isolated

and synthesized: delta-9-tetrahydrocannabinol (THC) was isolated in 1964 and synthesized in 1971, cannabidiol (CBD) was isolated in 1940 and synthesized in the 1990s, supporting an endogenous system implicated in the pharmacology activity of CBD ⁽⁶⁾.

There have been numerous reports in social media, surveys, preclinical studies and clinical trials of the efficacy of cannabis in the control and reduction of seizure frequency in TRE, especially in childhood resistant epilepsy. This is of great clinical importance since the repercussions of TRE are significant, with high rates of cognitive, behavioural and motor delays. This narrative review aims to summarize the existing literature regarding the efficacy of cannabinoids in seizure control.

Cannabis is a plant from the Cannabaceae family, which includes 170 species grouped in about 11 genera, which has three main species, *Cannabis sativa*, *C. indica*, and *C. ruderalis*. These plants contain over a hundred biologically active chemicals, known as cannabinoids, with the most abundant and best characterized being THC and CBD ⁽⁷⁾. THC is the major psychoactive constituent of cannabis, whereas CBD lacks psychoactive properties and has a low tolerance development rate. This is why CBD is considered to have a much wider therapeutic potential for epilepsy than THC ^(8,9).

The understanding of the pharmacological activity of cannabinoids has increased greatly since the discovery of the cannabinoid (CB) receptors and the endocannabinoid system. Cannabinoids exert their function through the interaction with CB receptors found in the CNS and in the periphery. Two main CB receptors have been identified, CB1 is primarily located in the brain, whereas CB2 is expressed in peripheral nervous tissues and its distribution is predominantly associated with the immune system, such as the spleen and skin ^(10,11). Both receptors belong to the class of G-protein coupled receptors which act on the second messenger system leading to intracellular effects: inhibition of the adenylyl cyclase enzyme leading to decreased levels of cAMP, stimulation of potassium channels leading to an increased efflux of potassium, and inhibition of voltage-gated calcium channels which decreases calcium influx ⁽¹²⁾. Anandamide and 2-arachidonoyl glycerol (2-AG) are the main brain endocannabinoids. They are small fatty acid derivatives of arachidonic acid. Unlike conventional neurotransmitters, they are not stored in vesicles but rather produced in the intracellular environment when neuronal activity triggers an enzyme ^(13,14).

It has previously been established that endocannabinoids are produced under conditions of increased neuronal excitability and specific intracellular signalling. Therefore, during an epileptic seizure where there are large changes in transmembrane voltage, intracellular calcium increases and neurotransmitters such as acetylcholine and glutamate are released, a release of endocannabinoids is triggered ⁽¹⁰⁾. There is evidence in many studies that exogenous cannabinoids can be neuroprotective and that CB1 activation by the seizure-induced release of endocannabinoids is also neuroprotective ^(10,15-17). The purpose of this study is to perform a narrative review of the literature to find out the current evidence about the usage of phytocannabinoids for TRE.

METHODS

A search was performed in MEDLINE (through Pubmed) using MeSH terms and free texts to identify articles regarding the use of cannabis and its compounds in the treatment of epilepsy. The first search was conducted on November 13, 2018 and conducted again on March 29, 2019. There were no language or year of publication restrictions. The following search strategy was used:

"Marijuana"[Mesh] OR "Ganja"[All Fields] OR "Hashish"[All Fields] OR "Hemp"[All Fields] OR "Bhang"[All Fields] OR "Cannabis"[Mesh] OR "Cannabinoids"[Mesh] OR "Cannabinol"[Mesh] OR "Dronabinol"[Mesh] OR "Tetrahydrocannabinol"[Mesh] OR "Cannabis"[All Fields] OR "Marihuana"[All Fields] OR "Marijuana"[All Fields] OR "CBD"[All Fields] OR "THC"[All Fields] OR "Medical marijuana"[Mesh] OR "Marijuana use"[Mesh] OR "Cannabinol"[All Fields] OR "Cannabinoids"[All Fields] OR "Tetrahydrocannabinol"[All Fields] OR "Dronabinol"[All Fields] AND "Epilepsy"[Mesh] OR "Epilepsy"[All Fields] OR "Seizures"[Mesh] OR "Seizures"[All Fields] OR "Epilepsies"[All Fields]

RESULTS

The search retrieved 868 references, the titles, and abstracts of systematic reviews, meta-analysis, case reports, review articles, and clinical trials were screened and the 42 which were considered most relevant were used for data extraction.

Preclinical studies: CBD and THC were found to be ineffective for animal-model absence seizures, but they were effective against cortical focal seizures, limbic seizures, and tonic-clonic seizures. In animals with pilocarpine-induced temporal lobe epilepsy, pre-treatment CBD reduced tonic-clonic seizures, without influencing mortality. THC and CBD were effective against limbic seizures produced by repetitive electrical stimulation in animal models ⁽¹⁸⁾.

Karler et al., in 1987, found that THC had an anticonvulsant effect in various tests, however, it was proconvulsant in 2 other tests. Therefore THC could exert not only a depressant but also an excitatory effect ⁽¹⁹⁾.

A study was performed to determine whether endocannabinoid signalling is affected in the epileptic human hippocampus. To this end, hippocampal samples were obtained from patients with therapy-resistant temporal lobe epilepsy (TLE), and an analysis of the molecular components of the endocannabinoid system was analysed; CB1 receptor expression and the fraction of glutamatergic axon terminals equipped with CB1 were down-regulated in the epileptic hippocampus ⁽²⁰⁾. In patients with refractory mesial TLE, it was also noted that the endocannabinoid system and CB1 receptor were altered, suggesting a role in the pathophysiology of epilepsy ⁽²¹⁾.

Clinical studies: The characteristics and conclusions of the relevant secondary studies, which were identified, are included in Table 1. One systematic review and meta-analysis found that patients who suffered from Lennox Gastaut syndrome or Dravet syndrome had a reduction in seizure frequency as compared to placebo. However, these patients experienced more adverse events ⁽²²⁾. Another systematic review found seizure reduction in patients with Lennox Gastaut syndrome ⁽²³⁾. There is some evidence that cannabinoids may reduce seizure frequency among children with drug-resistant epilepsy, however, this has only been evidenced for CBD and is not clear for other cannabinoids ^(24,25).

Some of the studies identified a lack of adequately conducted trials regarding the efficacy of cannabinoids as a treatment for epilepsy ^(25,26). One of the included systematic reviews concluded that "no reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy", owing to the lack of data from randomized, controlled trials of CBD, THC or other cannabinoids ⁽²⁶⁾.

Primary studies of multiple types were included. Their characteristics and main results are shown in

Table 2. Three primary studies that were not included in the systematic reviews were retrieved. The three of them were prospective open-label trials and in all of them, there was a decrease in seizure

frequency⁽²⁷⁻²⁹⁾. In one of these studies, an increase in seizure frequency was identified in a small number of patients. In this trial, both CBD and THC preparations were given⁽²⁹⁾.

Table 1. Characteristics of included secondary studies

Author / Year	Type of review	Population	Included studies	Design	Intervention	Main results
Lattanzi, et al. 2018 ⁽²²⁾	Systematic Review and meta-analysis	Pediatric and/or adult age, diagnosis of epilepsy, and seizures uncontrolled by concomitant AEDs, with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS)	Four trials	Randomized, double- or single-blinded, placebo-controlled, parallel-group add-on studies with active and control arms	Oral CBD	Adjunctive CBD in patients with LGS or DS experiencing seizures uncontrolled by concomitant anti-epileptic treatment regimens is associated with a greater reduction in seizure frequency and a higher rate of AEs than placebo.
Lattanzi, et al. 2018 ⁽²³⁾	Systematic review and meta-analysis	Patients of any gender, any ethnicity, paediatric and/or adult age, and diagnosis of LGS	Two trials	Randomized, placebo-controlled, single- or double-blinded trials	Cannabidiol	Adjunctive CBD resulted in a greater reduction in seizure frequency and a higher rate of AEs than placebo in patients with LGS presenting seizures uncontrolled by concomitant AEDs
Elliot, et al. 2018 ⁽²⁴⁾	Systematic review	Children with epilepsy treated with cannabis-based products	Four RCTs and 19 NRSs were included	Randomized controlled trials and non-randomized studies	Cannabis-based products	Cannabidiol probably reduces seizures among children with drug-resistant epilepsy (moderate certainty). At this time, the evidence base is primarily limited to cannabidiol, and these findings should not be extended to all cannabis-based products
Stockings, et al. 2018 ⁽²⁵⁾	Systematic review	Patients of any age, with any type of epilepsy or seizure	6 randomised controlled trials (RCTs), 30 observational studies	RCTs, non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies, analytical cross-sectional studies, self-report surveys, and case reports	Plant-based and pharmaceutical cannabinoids	Few high-quality RCTs have been conducted to date, and those that currently exist have tested CBD in paediatric samples with rare and serious forms of drug-resistant epilepsy. Of these existing studies, a reasonable proportion of patients experienced a decrease in seizure frequency when using pharmaceutical grade CBD products in addition to AEDs; however, minor AEs were likely and complete seizure freedom was unlikely.
Gloss & Vickrey 2014 ⁽²⁶⁾	Systematic review	People of any age or sex, with epilepsy of any type	four randomized trials	Randomized controlled trials (RCTs) whether blinded or not	Any type of marijuana, synthetic or natural THC, cannabidiol, cannabidiol, or combinations that include these agents, for ingestion or inhalation for the control of seizures	No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients generally for short periods of time, and so the safety of long term, cannabidiol treatment cannot be reliably assessed

Source: by the authors

Table 2. Characteristics and main results of included primary studies

Author / Year	Study Type	Number of participants/ Doses	Results
Cunha et al ⁽⁹⁾ 1980	Prospective, placebo-controlled trial of treatment-resistant epilepsy participants, followed for up to 4.5 months	15 participants; treatment: 8, placebo: 7. CBD doses 200-300 mg/daily	Of the CBD group, 4 showed clinical improvement, of the placebo group none showed improvement.
Hess et al ⁽³⁰⁾ 2016	Case series of patients with TRE and a diagnosis of TSC received CBD for at least 6 months	18 participants. 5 mg/kg/ daily increased up to maximum dose of 50 mg/kg/day	There was a median percent change in weekly seizures of 48.8%. 4 patients had a percent decrease in seizures of >80%. 2 had a decrease of >90%
Maa and Figi ⁽³¹⁾ 2014	Case report of 5-year-old girl with Dravet syndrome	1 participant treated with cannabis extract	>90% of reduction in the frequency of generalized tonic-clonic seizures
Tzadok et al ⁽³²⁾ 2016	Retrospective case series of children and adolescents with refractory epilepsy in 4 centres in Israel. Followed for 3-12 months	74 patients treated with CBD-enriched oil at a dose of 1-20 mg/kg/day	Most of the patients reported a reduction in seizure frequency (74.9%). 13 had a 75-100% reduction, 25 a 50-75% reduction, 9 had a 25-50% reduction and 19 had a <25% reduction
Devinsky et al ⁽³³⁾ 2017	Multicentric, double-blinded randomized placebo-controlled trial of children and young adults with Dravet syndrome and TRE	108 participants. 52 in the cannabidiol group and 56 in the placebo group	In the cannabidiol group, the median change of convulsive seizure frequency reduction was of 38.9%, in the placebo group the median change was of 13.3%
Kaplan et al ⁽³⁴⁾ 2017	Prospective case series of patients with TRE and Sturge Weber syndrome	3 participants were given Epidiolex at a dose of 5-25 mg/kg/day	Seizure frequency was significantly decreased. All subjects reported improvement in quality of life
Vezyroglou et al ⁽²⁷⁾ 2017	Prospective, open-label trial of children with TRE. Followed for 8 weeks	23 participants were given CBD at a dose of up to 16 mg/kg/day	47.8% of participants reported a >50% seizure reduction
Neubauer et al ⁽³⁵⁾ 2018	Retrospective case series of children and young adults with TRE, followed for 6 months	66 participants were given CBD to a maximum dose of 16 mg/kg/day	48.5% of patients had a 50% improvement or higher, 21.2% became seizure free
McCoy et al ⁽²⁸⁾ 2018	Prospective open-label trial of children with Dravet syndrome, followed for 20 weeks	14 participants were given CBD and THC preparations at 50:1 ratio, to a max dose of 16 mg/kg/day CBD	50% responder rate was 63% overall, 47% of participants had a reduction rate of 50-90%, 16% of >90%. 4 patients reported an increase in seizure frequency
Szaflarski et al ⁽²⁹⁾ 2018	Prospective open-label expanded access program of children and adults with TRE. Followed for 12 weeks	607 patients were given Epidiolex with a maximum dose of 25-50 mg/kg/day	Median monthly seizure frequency of convulsive seizures was reduced by 51% and the frequency of total seizures was reduced by 48%
Thiele et al. ⁽³⁶⁾ 2018	Multicentric, randomised, double-blind, placebo-controlled trial of Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome.	171 patients. 86 received cannabidiol and 85 received Placebo.	The median percentage reduction in monthly drop seizure frequency from baseline was 43.9% (IQR -69.6 to -1.9) in the cannabidiol group and 21.8% (IQR -45.7 to 1.7) in the placebo group. Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group; most were mild or moderate.

Table 2. Characteristics and main results of included primary studies (Continuación)

Author / Year	Study Type	Number of participants/ Doses	Results
Devinsky et al. ⁽³⁷⁾ 2018	Multicentric double-blind, placebo-controlled trial of patients with the Lennox-Gastaut syndrome (age range, 2 to 55 years) who had had two or more drop seizures per week during a 28-day baseline period.	225 patients. 76 received 20-mg cannabidiol, 73 received 10-mg cannabidiol, and 76 received placebo.	The median percent reduction from baseline in drop-seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group (P=0.005 for the 20-mg cannabidiol group vs. placebo group, and P=0.002 for the 10-mg cannabidiol group vs. placebo group). The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite, and diarrhoea; these events occurred more frequently in the higher-dose group.
Devinsky et al. ⁽³⁸⁾ 2018	Multicentric prospective, open-label trial (not controlled) of patients aged 1-30 years, with intractable childhood-onset epilepsy.	162 patients in the safety and tolerability analysis, 137 patients in the efficacy analysis. Patients were given oral cannabidiol at 2-5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site).	Adverse events were reported 79% of the patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhoea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). The median reduction in monthly motor seizures was 36.5% (IQR 0-64.7)

Source: by the authors

A multicentric open-label interventional study was performed which included 137 patients with TRE -including patients with a diagnosis of Dravet syndrome and Lennox Gastaut syndrome- who received CBD at a maximum dose of 25-50 mg/kg/day. There was a motor seizure reduction of 36.5% and 4% of patients were free of motor seizures during the 12 week treatment period⁽³⁸⁾.

The lack of a placebo control group and risk of bias reduce the strength of conclusions that can be drawn from this study⁽³⁹⁾.

Rosenberg et al reported the results of 137 patients with intractable childhood-onset epilepsy who received oral cannabidiol. The median reduction in motor seizures while receiving CBD was 36.5% (interquartile range 0-64.7)⁽³⁹⁾.

GW Pharmaceuticals along with other investigators are performing placebo-controlled randomized clinical trials, some evaluating the efficacy of Epidiolex (purified CBD) in forms of TRE. Recently the data regarding the first adequately-controlled phase 3 clinical trial of Epidiolex in patients with Dravet syndrome was published. It included 120 patients who were randomly assigned to receive Epidiolex at a dose of 20 mg/kg/day or placebo. Of the patients in the treatment group, 43% experienced at least a 50% reduction in seizure frequency, whereas in the placebo group the reduction was 27%⁽⁴⁰⁾.

Several patient and caregiver surveys have evaluated the efficacy of cannabis in epilepsy. In one survey of 117 caregivers assessing the efficacy and side effects of CBD exposure in children with infantile spasms and

Lennox Gastaut syndrome, 5 respondents reported an increase in seizure frequency, 11 reported no change, and 100 (85%) reported a reduction in seizure frequency, 16 of those reporting complete seizure freedom⁽⁴¹⁾. Another survey performed in 2015 to 75 parents whose children were treated with oral cannabis extract in Colorado, reported that 33% of the patients had a seizure reduction frequency of more than 50%, although these responses were not associated with improvements in interictal EEG (electroencephalogram) when available⁽⁴²⁾.

DISCUSSION

The interest in the use of cannabis as a treatment for epilepsy has increased over the last decades. In the early 1970's several researchers found that CBD could reduce or block seizures in animal models⁽⁴³⁾. These models provide powerful assays to validate the efficacy of cannabinoids in preventing seizures and reducing mortality in epilepsy⁽³⁹⁾. The preclinical studies included in this review provide an explanation for the preferential use of CBD over THC in clinical studies, as THC has excitatory effects⁽¹⁹⁾. This has also been evidenced in the increase in seizure frequency in patients of one observational study in which preparations containing THC were used⁽²⁸⁾.

On the other hand, CBD has been observed to have antiepileptic activity in preclinical studies with animal models, as well as clinical studies, making it the cannabinoid with more available evidence for the treatment of epilepsy. However, the clinical evidence supporting the use of CBD in epilepsy is limited, as few adequately-designed trials exist, and most address only paediatric patients^(24-26,39).

There are ongoing placebo-controlled randomized clinical trials especially addressing childhood refractory epilepsy syndromes, which have suggested that cannabis-based treatments might be effective. This novel therapeutic agent is warranted to be studied further, as it may have fewer adverse effects than conventional AEDs and produce an improvement in the quality of life of the patients.

Although this review included a large number of studies, its findings may be somewhat limited by the non-systematic nature of the review. Furthermore,

a high proportion of the included evidence comes from observational studies, which limits the certainty concerning the effectiveness of cannabinoids in epilepsy.

CONCLUSIONS

Cannabinoids as a treatment for seizures is a novel therapy and it offers hope for patients with refractory epilepsy. Nonetheless, it is important to highlight that this therapy has not proven to be effective in all kinds of patients and therefore, it should not be used without a clear medical indication. The evidence we have so far from clinical studies have demonstrated the efficacy of CBD in the decrease of seizures, predominantly in patients diagnosed with Lennox Gastaut and Dravet syndrome.

Although few studies are evaluating the efficacy of cannabinoids in epileptic encephalopathies described previously, there are many studies which evaluate the quality of life of the patients using CBD, this has shown significant improvement, reducing not only seizures but improving motor and behavioural symptoms as well.

Another point of debate is the use of CBD as a monotherapy or as an add-on therapy, the literature suggests that we should not stop the baseline treatment of the patient, but use CBD in combination with other anticonvulsants, especially clobazam since this has shown to be the most effective in reducing seizures.

Despite the evidence mentioned in this review supporting the efficacy of cannabidiol-based therapies in treatment resistant epilepsy in children, there is little evidence and a lack of high-quality studies supporting the efficacy in adult population.

Therefore, there is a need for adequately designed clinical trials, especially in this population. Further research is needed to adequately establish the safety and effectiveness of cannabinoids in the treatment of epilepsy.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

FINANCING

This study did not receive funding.

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